

Total serum tryptase levels are higher in young infants

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Abstract

Background: Mast cells participate in immune defense and allergic disease. At baseline, serum tryptase levels primarily reflect mast cell burden, while mast cell degranulation leads to granule tryptase release, which may be detectable as a transitory elevation of serum tryptase levels. Thus, mast cell burden and mast cell activity are reflected by serum tryptase levels, but reports are scarce in infants under 1 yr. We aimed at defining levels of total serum tryptase levels in this population.

Methods: Total serum tryptase levels (ImmunoCAP; Phadia) were measured in 372 sera from infants younger than 1 yr. Two hundred and forty-two sera came from non-atopic, non-allergic infants in good condition, who had blood drawn for routine follow-up or diagnosis of illnesses that are not known to induce changes in serum tryptase levels. Seventy-two sera were from atopic and/or allergic infants, and 58 sera were from non-atopic, non-allergic infants requiring intensive care.

Results: Median serum tryptase levels were highest in infant2s under 3 months ($6.12 \pm 3.47 \mu\text{g/l}$) and gradually decreased before reaching levels similar to those described in adults and older children ($3.85 \pm 1.8 \mu\text{g/l}$ between 9 and 12 months). Atopic/allergic status was associated with even higher tryptase levels ($14.20 \pm 10.22 \mu\text{g/l}$ in infants younger than 3 months). Intensive care patients had lower levels of serum tryptase ($4.12 \pm 3.38 \mu\text{g/l}$ in infants younger than 3 months). Longitudinal follow-up was performed in 27 patients and showed tryptase levels decrease over time in individual patients. Infants' sex was not found to interfere with serum tryptase levels.

Conclusion: Total serum tryptase levels are significantly higher in younger infants compared with older ones. In infants of the same age, serum tryptase levels may vary according to the clinical condition and thus suggest mast cell involvement in the physiologic as well as in the allergic immune responses of young infants.

Tryptases are a group of serine peptidases highly abundant in the granules of human and animal mast cells (1–4). There are two major human tryptases, α and β , with β -tryptase being the most prominent one. Enzymatically active β -tryptase tetramers are stored in mast cell granules. At baseline, low levels of tryptase zymogen forms (α/β protryptases) released by mast cells are detectable in the bloodstream. Therefore, baseline serum tryptase levels are mainly an

indicator of an individual's mast cell burden. Mast cell granule content is promptly exocytosed after mast cell activation through either immunoglobulin E-dependent (allergy) or immunoglobulin E-independent (bacterial) stimuli (reviewed in Ref. 3). Mast cell degranulation results in mature α/β tetramer release into the bloodstream, along with vasoactive amines like histamine and serotonin, mature forms of cytokines such as tumor necrosis factor- α (TNF- α) and interleukin-4 (IL-4). Upon release, tryptases take part in extracellular matrix degradation and remodeling, expression, and secretion of inflammatory mediators (5), neutrophil and eosinophil chemotaxis (6), monocyte and macrophage

Abbreviations

AA, atopic and/or allergic; NA, nonatopic and nonallergic; ICU, intensive care unit.

activation, fibroblast proliferation, and collagen synthesis (2), thus participating in inflammatory and immune responses. Among the great number of mast cell products involved in the recruitment and activation of other immune cells, tryptases have the advantage of being virtually specific of mast cells. Because mast cells have been recognized as sentinel cells of the innate immunity (7), monitoring their activation status is a challenging issue. Mast cells reside at host–environment interfaces, effectively sense pathogens, phagocytose bacteria, and initiate inflammatory and immune responses. Because mast cell maturation is microenvironment specific (7), there is a rich array of mast cell-induced immune responses. Little is known about mast cell contribution to infant immunity, although these phylogenetically old cells are rapidly effective for first-line defense, for antigen presentation, and for the induction of adaptive immune responses.

There is only one commercial assay that measures serum tryptase (ImmunoCAP tryptase; Phadia, Uppsala, Sweden). The ImmunoCAP assay measures both immature and mature α/β tryptases and is therefore referred to as the total tryptase level (1). A monoclonal antibody has been prepared, which specifically recognizes only mature forms of α/β tryptases, thus distinguishing between the basal mast cell secretion of immature tryptase and the activation-induced degranulation leading to elevated serum levels of mature tryptase, but this antibody is not commercially available (4). Measuring the total serum tryptase levels is a convenient, although imperfect, way to monitor mast cell burden and mast cell activation status. First, tryptases are highly specific of mast cells. Basophil granules contain very low amounts of tryptases, <1% compared to mast cells (8). Second, the half-life of serum tryptase is around 2 hr after mast cell degranulation, which makes blood collection easier in case of anaphylaxis management. Third, tryptase levels are stable in blood samples stored at +4°C or even at room temperature (9). Tryptase stability and a good correlation between histamine and tryptase release during anaphylaxis have led to widespread use of serum tryptase measurement in anaphylaxis management (10). Baseline serum tryptase levels are informative in cases of mastocytosis (11), malignancies (12, 13), allergies to Hymenoptera venoms (14, 15), and probably some other cases (16).

Yet little information on tryptase levels in infants and children is available. We and others (17, 18) recently reported that serum tryptase levels in children were similar to those previously established in adults. Additionally, our group found that serum tryptase levels in infants younger than 3 months were twice as high as those measured in older ones (17), but the small dimension of the group did not allow us to draw sound conclusions. We therefore sought to examine serum tryptase levels in a larger sample of infants, with special focus on infants younger than 6 months. Serum tryptase level was measured in 372 consecutive infants aged <1. We confirm here that total serum tryptase levels are significantly higher in infants younger than 3 months and gradually decrease during the first year of life. This pattern of total serum tryptase kinetics was demonstrated in infants irrespective of their clinical condition: non-atopic/non-allergic (NA), atopic/allergic (AA), and critically ill

(ICU) infants. Moreover, AA infants display even higher levels, while ICU infants present with lower levels when compared to NA infants in good or moderate condition.

These findings suggest that higher levels of tryptase in young infants might reflect not only mast cell propensity to respond to IgE-mediated stimuli, but also a physiologic contribution to infants' immunity. Despite the drawback of a measurement which might not represent the true baseline, as infants had their blood collected during various medical settings, elevated levels of serum tryptase might open a new window on the role of mast cells in infants' immunity.

Materials and methods

Patients and blood samples

Three hundred and seventy-two serum samples were tested for tryptase levels from March 2008 through June 2010. Sera were collected consecutively from outpatient and inpatient infants younger than 12 months, attending pediatric care departments in Assistance Publique Hôpitaux de Marseille. Excess serum available after routine laboratory work-up in the Biochemistry or Immunology Laboratories was used for total tryptase level determination. Infants belonged to one of three clinical settings:

The non-atopic/non-allergic group (NA) comprised 242 sera from outpatients and inpatients either in good condition or with moderate disease excluding allergy and atopy, which should not have interfered with tryptase levels, e.g., acute diarrhea, ear–nose–throat complaints, and chronic neurologic pathologies.

The atopic/allergic group (AA) comprised 72 sera from outpatients and inpatients whose illness was linked to an allergy and/or atopy diagnosis established by a pediatric allergologist. Symptoms included food-induced eczema, urticaria, vomiting, abdominal pain, diarrhea, failure to thrive, wheezing, and other respiratory symptoms. These are immediate and/or delayed symptoms of food-induced allergic reactions (19). All children in the AA group displayed elevated total IgE at least twice the highest normal value for the age group considered (> 50 $\mu\text{g/l}$ before 3 months, > 75 $\mu\text{g/l}$ between 3 and 6 months, > 150 $\mu\text{g/l}$ between 6 and 12 months) and/or specific IgE ≥ 0.5 kU/l to clinically relevant allergens (cow's milk extract and proteins in the vast majority of cases, soy, egg white, peanut).

The intensive care unit (ICU) group comprised 58 sera collected from patients with serious conditions, e.g., neonatal jaundice, severe diarrhea, organ transplantation, severe infection, and requiring intensive care at the time of blood collection.

Mastocytosis, systemic anaphylaxis, hematologic malignancies, cardiology, and trauma patients were not included. Ethnic origin enquiries are not allowed in France, but our hospital's recruitment is representative of the region's Mediterranean inhabitants.

Laboratory work-up

Total serum $\alpha + \beta$ tryptase and total and specific IgE levels were measured with an ImmunoCAP 250 machine and the

corresponding reagents (Phadia). The calibration curves, quality controls, internal, and external controls were carried out regularly during routine activity. Total tryptase levels were expressed as micrograms per liter. Specific IgE levels were detectable above a threshold of 0.1 kU/l. Total IgE levels were expressed as kUI/l, with 1 kUI = 2.4 µg/l total IgE.

Expression of results

Results were expressed as the median ± interquartile range. The normality test showed that the results did not follow a normal law. A Kruskal–Wallis analysis on groups NA, AA, and ICU was then performed and yielded a *p* value of 1.96×10^{-9} , allowing the pursuit of statistical analysis. For the study of age and clinical condition influence on tryptase levels, statistical comparison was performed using Wilcoxon's test, and the significance level was set at *p* ≤ 0.05.

Results

Demography

Infants' characteristics of age, sex, and clinical condition are summarized in Table 1. Half of the NA and AA, and 75% of the ICU patients were younger than 4 months. Male and female patients were grossly equivalent among NA infants, while AA and ICU populations were made up of 60% men.

Serum tryptase levels and infants' age in NA infants

Median serum tryptase results were expressed as a function of age (Fig. 1). Infants younger than 3 months presented with median serum tryptase levels of 6.12 ± 3.47 µg/l, which was significantly higher compared to infants aged 3–12 (4.42 ± 2.44 µg/l, *p* = 4×10^{-7}), and also to infants aged 3–6 months (5.32 ± 3.26 µg/l, *p* = 0.05), 6–9 months (4.25 ± 2.19 µg/l, *p* = 7×10^{-5}), and 9–12 months (3.85 ± 1.8 µg/l, *p* = 6×10^{-7}). Median serum tryptase lev-

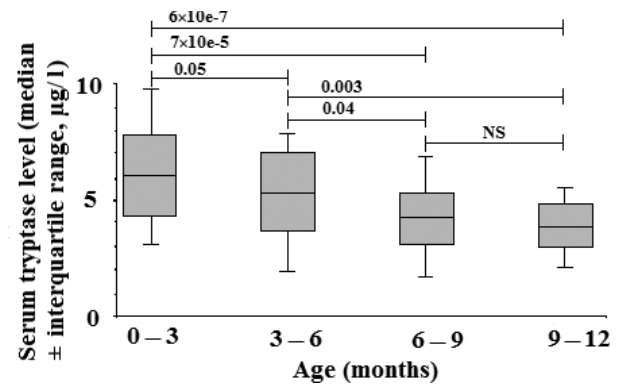


Figure 1 Serum tryptase levels as a function of 3-month age groups from birth to 12 months (median ± interquartile range). Younger infants display higher tryptase levels (*p* values are shown).

els decreased over time, with higher values in 3- to 6-month-old infants compared to 6- to 9-month-old ones (*p* = 0.04) and to 9- to 12-month-old ones (*p* = 0.003). Serum tryptase levels tended to become stable after 6 months, with no significant difference found between the groups 6–9 and 9–12 (*p* = 0.24).

To obtain a more accurate analysis of tryptase levels as a function of age, results were split into 1-month groups of age (Fig. 2a). Median serum tryptase levels were twice as high in infants younger than 1 month when compared to infants aged 11–12 months (6.17 ± 3.31 µg/l vs. 3.15 ± 1.46 µg/l, *p* = 6×10^{-8}), and all results followed a downward trend line. Given the widespread reporting of mean serum tryptase values in numerous other studies and for a direct comparison to the authors' earlier study in mean values (17), mean ± standard error of the mean are represented in Fig. 2b.

Because the highest serum tryptase levels were measured in youngest infants, we further took a closer look at their evolution by means of 10-day groups covering the first 4 months (Fig. 2, insert). The neonatal period was split into a 0- to 4-day group and a 5- to 10-day group, to exclude a potential contribution of placental mast cells. Median serum tryptase levels were lower (3.51 ± 1.2 µg/l) during the immediate post-natal period, then rapidly increased, reached a plateau around 6 µg/l, and slightly decreased.

To check whether group results also held for individual patients, we compared serum tryptase levels of infants for whom more than one time point was available. Such a comparison of serum tryptase levels was available for 27 infants (Fig. 3). In 18 cases (67%), serum tryptase levels measured at earlier time points were higher than those measured at later time points, and in nine cases (33%), tryptase levels were stable or higher at the later time point. Median time between two serum tryptase determinations was 3 months in either case, ranging from 1 to 7 months for those whose serum tryptase levels had decreased and from 1 to 8 months for those whose serum tryptase levels had been stable, had fluctuated, or had increased.

Taken together, these results indicate a transient elevation of serum tryptase levels in NA young infants, starting during

Table 1 Infants' age, sex, and clinical status

Age (months)	Total number per age group	Nonatopic/nonallergic		Atopic/allergic		Intensive care unit	
		Total	Male	Total	Male	Total	Male
0–1	78	37	19	10	7	31	16
1–2	52	40	18	8	4	4	6
2–3	43	28	14	9	4	6	3
3–4	36	30	14	2	2	4	2
4–5	27	15	4	9	8	3	2
5–6	22	14	12	6	2	2	2
6–7	24	18	6	3	2	3	1
7–8	25	15	7	5	1	5	3
8–9	15	10	6	5	5	0	0
9–10	17	12	10	5	4	0	0
10–11	15	10	4	5	2	0	0
11–12	18	13	10	5	1	0	0
All ages	372	242	124	72	42	58	35

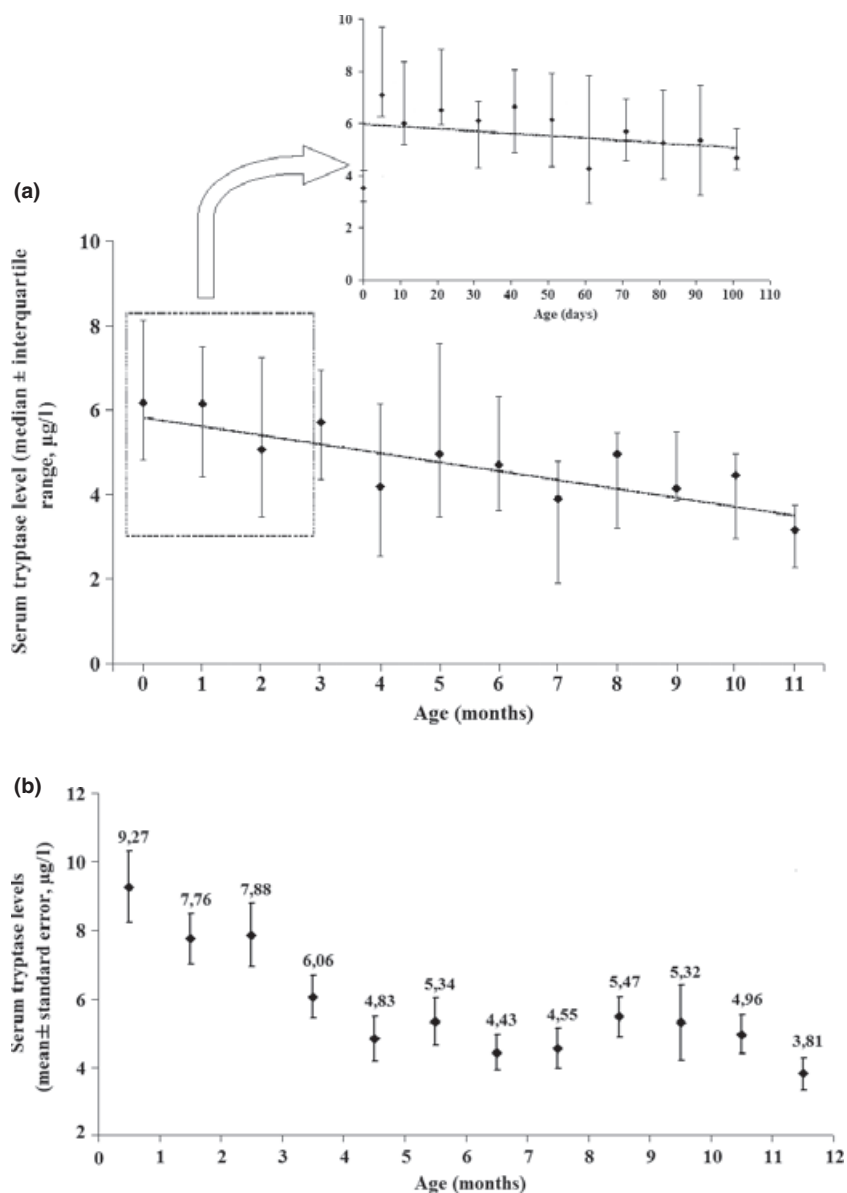


Figure 2 (a) Serum tryptase levels as a function of 1-month age groups from birth to 12 months (median \pm interquartile range and trend line). Insert: serum tryptase levels in infants aged 0–3 months, showing low values at birth and a rapid increase followed by a plateau. (b) The same data expressed as the mean \pm standard error of the mean.

the first week after birth, plateauing until the end of the second month of life, and then slowly decreasing.

Serum tryptase levels and atopic/allergic status

Because mast cells are known to be involved in allergic symptoms, we sought to find out whether our findings in NA infants also applied to AA ones. Median serum tryptase level was $14.2 \pm 10.22 \mu\text{g/l}$ in AA infants aged 3 months or less, but no more than $4.98 \pm 3.91 \mu\text{g/l}$ in AA infants aged 3–6 months ($p = 5 \times 10^{-5}$, Fig. 4a), $5.77 \pm 3.15 \mu\text{g/l}$ in 6- to 9-month-old AA infants ($p = 8 \times 10^{-5}$), and $5.84 \pm 3.57 \mu\text{g/l}$ in 9- to 12-month-old AA infants ($p = 2 \times 10^{-4}$). Taken together, these results confirmed the transient elevation of serum tryptase levels in infants younger than 3 months.

Moreover, AA infants aged <3 months presented with serum tryptase levels twice as high as those of NA infants of the same age group ($p = 5 \times 10^{-9}$, Fig. 4a). Serum tryptase levels in AA infants were also higher than in NA infants in the 6- to 9- and 9- to 12-month-old groups ($p = 0.05$ and 0.01 , respectively). These results were confirmed by detailed analysis with 1-month groups of age, showing significantly higher levels of median serum tryptase levels in all but three AA groups compared to NA groups ($*p \leq 0.04$, Fig. 4b).

Critical illness and serum tryptase levels

If mast cell activity were a key player in normal infants' immunity, then clinical conditions associated with impaired immune responses in this population should be associated

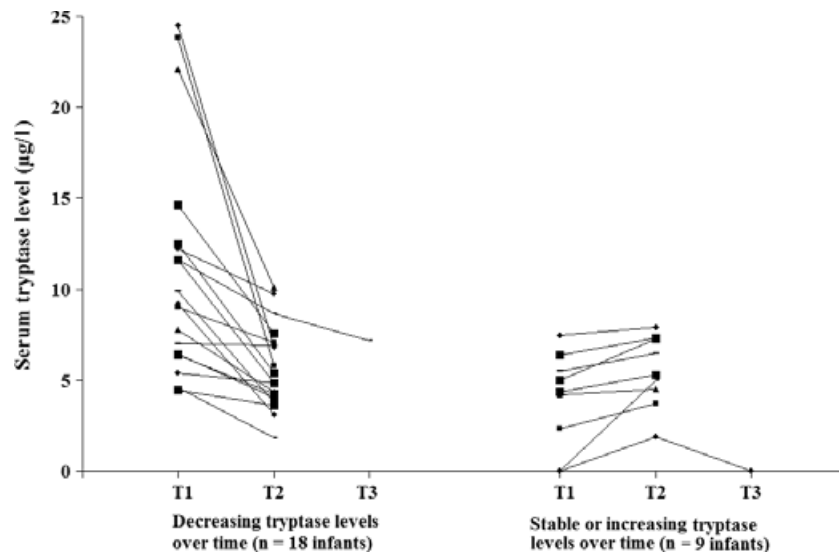


Figure 3 Comparison of early and later serum tryptase levels in individual infants. Serum tryptase levels decreased over time in 18/

27 (67%) infants and remained stable or increased in 9/27 (33%) infants. T1, T2, T3, and different time points.

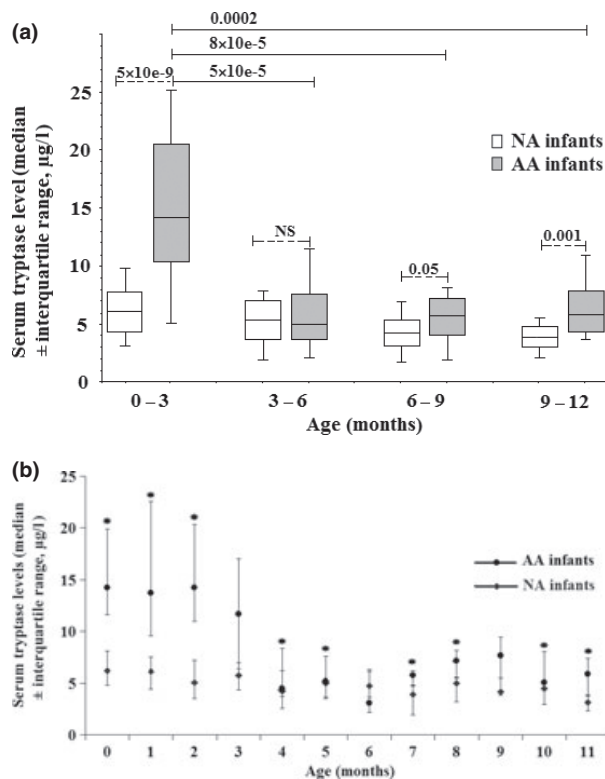


Figure 4 (a) Serum tryptase levels in atopic/allergic infants as a function of 3-month age groups (median \pm interquartile range) and comparison with results from non-atopic/non-allergic infants. (b) Serum tryptase levels in atopic/allergic infants as a function of 1-month age groups (median \pm interquartile range and trend line) and comparison with results from non-atopic/non-allergic infants. * $p \leq 0.04$.

with decreased mast cell function. We therefore sought to find out whether serum tryptase levels followed the same decreasing pattern in infants receiving intensive care for a variety of clinical conditions.

Serum tryptase levels of ICU patients indeed displayed a similar pattern, with higher values measured during the first 3 months of life ($4.12 \pm 3.38 \mu\text{g/l}$, $p = 0.001$ when compared with older infants, for details see Fig. 5a) followed by a gradual decrease over time. Moreover, levels were consistently and significantly lower than those found in NA patients (Fig. 5a). These findings were confirmed by the detailed analysis with 1-month groups, which also showed remarkably parallel trend lines in NA and in ICU infants (Fig. 5b).

Serum tryptase levels and infants' sex

Serum tryptase levels were analyzed as a function of sex in infants of each age group (0–12 months), and no difference was found (results not shown).

Discussion

We report here serum tryptase levels in a pediatric population aged < 1 yr. The main finding was a higher serum tryptase level in infants aged 3 months or less compared to older ones. This result held true for all infants, irrespective of their clinical condition: NA infants, as well as AA and ICU patients.

Atopic/allergic status was associated with even higher tryptase levels, especially in the youngest infants (0–3 months), while critically ill infants displayed lower tryptase levels.

The neonatal period was analyzed from birth to the fourth day and from the fifth to the tenth day of life. Because serum

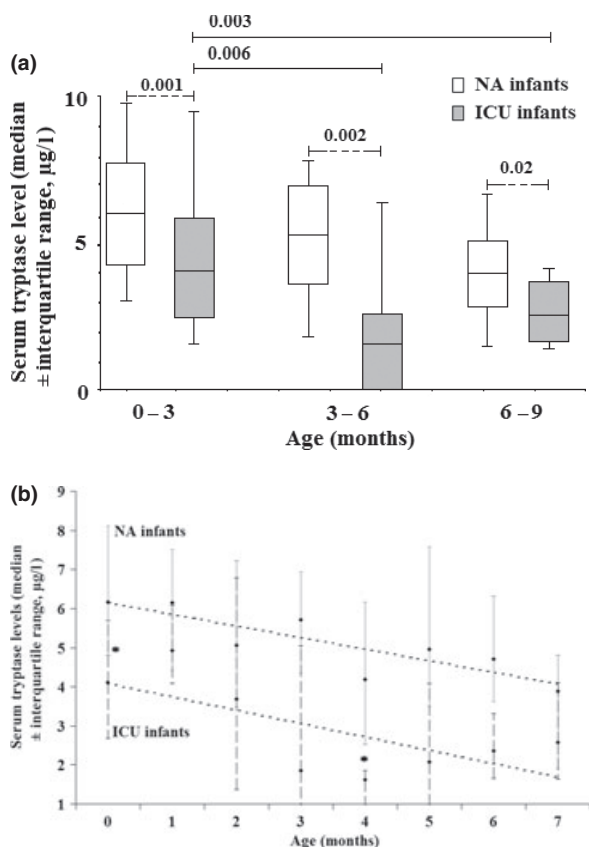


Figure 5 (a) Serum tryptase levels in critically ill infants as a function of 3-month age groups (median \pm interquartile range) and comparison with results from non-atopic/non-allergic infants. (b) Serum tryptase levels in critically ill infants as a function of 1-month age groups (median \pm interquartile range and trend line) and comparison with results from non-atopic/non-allergic infants. * $p \leq 0.04$.

tryptase levels were lower during the first 4 days of life ($3.51 \pm 1.2 \mu\text{g/l}$), the contribution of placental mast cells can be excluded. Moreover, serum tryptase half-life does not exceed 2 hr and thus is not in favor of prolonged placental mast cell-derived hypertryptasemia in infants. Serum tryptase rapidly increased during the first days of life and plateaued around $6 \mu\text{g/l}$ between 10 and 60 days. After the third month, median serum tryptase levels decreased to $4 \mu\text{g/l}$ and less, confirming previous findings in older infants (17, 18). In our previous study, results had been expressed as the mean \pm standard error of the mean, while in the current study, they are expressed as median \pm interquartile range, which was found more adequate for patient-derived data. Given the widespread reporting of mean serum tryptase values and for a direct comparison to these and our earlier study, Fig. 2b (NA infants) displays mean tryptase levels.

A child was considered atopic/allergic if at the precise time of the tryptase measurement he displayed clinical and biologic features of atopy/allergy. In our study, food allergy diagnosis was based on the association of symptoms and positive, specific IgE. Positive, specific IgE are defined as

superior to 0.1 kU/l with the ImmunoCAP method. We chose a slightly higher threshold value to improve specificity. A special remark on IgE cut-off values is needed here. They are often defined as the specific serum IgE levels (measured for a given allergen, with the ImmunoCAP method) corresponding to the 90%, 95%, or 100% positive predictive value for food allergy/for a positive provocation test. There is a high variability of such cut-off values, depending on the age, the presence or absence of atopic dermatitis, the amount of total IgE, the nature of the provocation test, and even the statistical tests (20). True food allergies may present with undetectable specific serum IgE (19). Small numbers of allergic children present with specific IgE above the cut-off values, that is, most of the allergic patients present with specific IgE levels below the cut-off levels. Serum tryptase levels in AA infants followed a similar pattern up to 4 months. Of note, median serum tryptase levels in AA infants aged 3 months or less were twice as high as those of NA infants ($14.2 \text{ vs. } 6.17$, $p = 5 \times 10^{-9}$). These AA infants presented with milk-induced immediate symptoms and in some case eczema. The youngest infant diagnosed with milk allergy was a 7-day-old boy with milk-induced vomiting, diarrhea and abdominal pain, positive skin-prick tests for the infant formula he was given, and milk IgE 0.77 kU/l . He and other infants diagnosed with cow's milk allergy were fed extensively hydrolyzed formulas and received allergologic follow-up. AA infants aged 6 months or more also presented with significantly higher serum tryptase levels compared to NA infants of the same age. In contrast, serum tryptase levels were similar in the 3- to 6-month-old groups of AA and NA infants. This result might be because of an insufficient number of AA sera (17 for this age group), but the hypothesis of a change in mast cell activity and/or in the pathophysiology of allergy at this time point cannot be excluded.

Higher levels of commercially measured total serum tryptase are usually believed to be a good marker of mast cell burden and mast cell activation, with mast cells being at the crossroad of immunity, inflammation, and anaphylaxis (3). Our results suggest mast cell activation might be a common finding in young infants, perhaps as part of the normal immune response during the first weeks of life. In line with this speculative hypothesis, we also found that critically ill infants presented with lower tryptase levels. In line with the hypothesis of a physiologic serum tryptase elevation in young infants, we found that in longitudinally followed infants serum tryptase levels generally decreased over time.

Massive involvement of cutaneous mast cells in urticaria neonatorum (toxic erythema of the newborn) was shown by Nelson et al. (21) as an innate immune response triggered by the encounter of the newborn with his/her future commensal microorganisms. Because mast cells are now recognized as sentinel cells at the frontiers of the organism, one may hypothesize on a physiologic activation of mast cells during the first weeks of life as a result of sustained immune stimulation.

Interestingly, stable tryptase levels during childhood seem to rise slowly during adulthood, reaching significantly higher levels after the age of 50 (22, 23). Whether mast cell burden

or mast cell activation, or both, is involved in this phenomenon is currently unknown. It might be speculated that mast cell activation accompanies the global proinflammatory changes in the aging human. More work with more sophisticated tools on larger pediatric and adult cohorts is needed in this direction.

In current practice, baseline tryptase levels are considered to be predictive of the clinical severity of an increasing number of atopic/allergic conditions, from anaphylaxis to atopic dermatitis (11–16). To our knowledge, true baseline serum tryptase levels have not been established in pediatric populations, because of specific ethical constraints. Our present study, as well as the previous ones (17, 18), has dealt with pediatric patients seeking medical care for various reasons. Despite this drawback, in our cohort, we found higher serum tryptase levels in atopic/allergic infants when compared to non-atopic/ non-allergic ones. This finding is in line with a previous study of our group (17), but not with results from the group of Komarow et al. (18), who studied 197 children aged 6 months to 18 yr and only found higher tryptase levels in atopic/allergic male patients compared to female ones. This discrepancy might be as a result of differences in the cohorts. For instance, both our present study and the previous one dealt with younger children: for the present study, we deliberately included only sera from infants under 1 yr, while in our previous study, we included patients up to 15 yr. Also, ethnicity was assessed in Komarow's study, but not in ours, according to French laws. Another point is that in our study, we chose to set the cut-off values for positive serum IgE slightly higher than the usual ones, to augment specificity. That is, patients with specific IgE levels between 0.1 and 0.49 kU/l were considered negative and so were total IgE levels less than twice the normal superior value. This might be an important point, because low-level sensitization is frequent in young infants, without reaching the threshold of clinical expression. Conversely, allergy symptoms in young infants may be overseen, as it is frequent even among medical staff to consider that allergy is unlikely in this age group, leading

to delayed diagnosis and thus paving the way for severe sensitization.

Higher serum tryptase levels in young infants, especially atopic/allergic ones, might also be a critical issue in the field of sudden infant death syndrome. Indeed, the hypothesis of mast cell involvement in sudden infant death syndrome, either through typical anaphylaxis or through bacterial activation of mast cells, is still awaiting confirmation. A possible link between serum tryptase levels and the occurrence of sudden infant death syndrome has been mentioned several times, based *inter alia* on the determination of *postmortem* tryptase (24–26). It is unclear whether serum tryptase levels are elevated or not in cases of sudden infant death syndrome, and if they are, whether mast cell activation is a cause, a result, or an epiphenomenon.

In conclusion, we show here that very young infants, aged 3 months or less, present with higher serum tryptase levels compared to older ones. Atopic/allergic infants display even higher serum tryptase levels, while critically ill infants have comparatively lower results, but in all groups serum tryptase levels are significantly higher in infants aged 3 months or less, then decrease over a few months' period of time. A possible association between mast cell activation and the physiologic immune response of young infants is therefore suggested. More work is needed to clarify biochemical (mature vs. immature tryptases), epidemiologic (true baseline tryptase determination), and clinical (mast cell monitoring, modulation, or stimulation) implications of our findings.

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Conflict of interest

Authors declare they have no conflict of interest in the publication of this paper.

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